

The Treatment of Chronic Obstructive Pulmonary Disease

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Abstract

In this study, new aspects of treatment of exacerbations of chronic obstructive pulmonary disease are presented based on vast clinical material and our own studies. According to the obtained data it can be concluded that the treatment of chronic obstructive pulmonary disease exacerbations is a complex process, oriented towards a multitude of pathogenic mechanisms of the disease. One of the pathogenic mechanisms of chronic obstructive pulmonary disease exacerbations is respiratory infection which makes the administration of the antibacterial drugs is an important component in the complex treatment of the disease. The administration of antibacterial therapy diminishes the hospitalization period of these patients and, as a result, reduces the total economical impact of the health management.

Key words: chronic obstructive pulmonary disease, complex treatment, antibacterial therapy.

Лечение обострений хронической обструктивной болезни лёгких

В работе представлены современные аспекты лечения обострений хронической обструктивной болезни лёгких, которые основаны на обширном клиническом материале и на основании собственных клинических исследований. На основании полученных результатов можно сделать вывод, что лечение обострений хронической обструктивной болезни лёгких представляет комплексный процесс, обусловленный воздействием множеством патогенетических механизмов данного заболевания. Один из патогенетических механизмов заболевания – респираторная инфекция, что обуславливает назначение антибактериальных препаратов в лечении обострений хронической обструктивной болезни лёгких. Дифференцированный подход к назначению антибактериальных препаратов приводит к уменьшению периода госпитализации пациентов и как следствие этого – к уменьшению экономических затрат при оказании медицинской помощи.

Ключевые слова: хроническая обструктивная болезнь лёгких, комплексное лечение, антибактериальная терапия.

Chronic obstructive pulmonary disease (COPD) is a disease which is characterized by a progressive, partial reversible bronchial obstruction, which results from airway inflammation in response to unfavorable external factors (smoking, occupational hazard, pollutants and others). It is established that in cases of COPD, morphological changes are observed in the central and peripheral branches as well as in the lung parenchyma. The result of epidemiological research shows that in Europe and North America 4 – 15% of the adult population suffers from COPD [1, 2]. Official data show that in the Russian Federation 2.4 millions patients with COPD are registered. But the data from epidemiological research leads us to believe that this number could be as high as 16 millions people [3]. The morbidity and the mortality of the patients with COPD increases all over the world, which is primarily related to a high smoking rate. It is shown that this disease affects 4 – 6% of males and 1 – 3% of females older than 40 years [4]. In Europe this is for the cause of death of 200-300 thousands people per year [1, 3].

Exacerbation is a stage of COPD course. It negatively affects the quality of a patient's life, leads to the progression of bronchial obstruction, and is often a cause of hospitalization that considerable increase to the cost of treatment. COPD exacerbations can also be a cause of death. Exacerbations take place approximately 1 – 4 times a year [3].

Exacerbation is an acute increase of symptoms, in comparison with the otherwise stable state of patients. The most

frequent exacerbation symptoms are difficult breathing, cough intensification, increase in the production of expectoration and the changes of its characteristics. These symptoms often demand a modification of the pharmaceutical treatment [2, 3, 4]. Their mechanisms are shown in tab. 1.

The exacerbations of COPD are often associated with acute respiratory infections of the upper respiratory tract. We observed intensification of wheezing, subjective reports of feeling pressure in the throat, peripheral edema (appearance of peripheral edemas, weight's increasing etc.), increasing of general weakness and disturbances of conscience. Throat pain and fever normally do not appear in the exacerbations of COPD, but if present, other diseases have to be excluded (pneumonia, pneumothorax, thromboemboli of pulmonary arteries etc.).

The Reasons of COPD – exacerbations are:

1. Infection: *H. influenzae*, *St. pneumoniae*, *M. catharralis* which correspond to 13 – 46%, 7 – 26% and 9 – 20%, respectively. *Enterobacteriaceae fam.* should be considered as a cause of COPD exacerbation if patients are older than 65 years, have concomitant chronic pathologies or if the peak expiratory flow (PEF) during the first second is less than 50%. In cases of bronchiectasis with a permanent production of purulent expectoration *P. aeruginosa* should be considered [5].

2. Pollutant (NO₂, Sulfuric dioxide, Ozone, hard particles).

3. Drugs (beta-blockers, sedatives, barbiturates etc.).

4. Cardiac insufficiency and heart rhythm disorders.

Table 1

Possible mechanisms for the development of symptoms of exacerbations of COPD

Symptoms	Mechanisms of Development	Comments
1. Progression of shortness of breath	<ul style="list-style-type: none"> Increased catabolism Bronchial obstruction <ul style="list-style-type: none"> a) mucosal damage, increased bronchial hyper-reactivity/bronchospasm b) the infiltration of inflammatory cells of the respiratory tract c) edema of the bronchial mucosa d) mucous hypersecretion with increase in viscosity leading to formation of mucous plugs, reducing mucociliary clearance e) the progressive worsening of the diffusion-perfusion gradient 	Consequence of systemic inflammation and acidosis in COPD. Associated with increased production of neutrophils' proteinases, bronchial epithelium endothelin-1, and colonization with bacteria (<i>H. influenzae</i>) and viruses. Increase in the number of CD8+ lymphocytes, neutrophils, eosinophils; associated with increased production of «proinflammatory» cytokines (IL-6, TNF α , RANTES, etc.), neurotransmitters (LTV-4) and increased expression of adhesion molecules (ICAM-1, E-selectin). It can occur by the bacteria (<i>H. influenzae</i> , <i>S. pneumoniae</i> , <i>Ps. aeruginosa</i>), viruses, pollutants. Enhancing blood flow on poorly ventilated areas can easily lead to a deterioration of gas exchange and growth of hypoxemia.
2. Increased sputum production	<ul style="list-style-type: none"> Hypertrophy of the mucous glands Hyperplasia of goblet cells Degranulation of goblet cells 	Arises as a result of neutrophils' inflammation and the action of proteases under various pollutants and microorganisms.
3. Appearance of purulent sputum	<ul style="list-style-type: none"> The accumulation of eosinophils and neutrophils 	Associated with increased production of proinflammatory cytokines and increased expression of adhesion molecules (see above), all of which can occur secondary to bacterial infection.

Note: IL - interleukin (s); TNF α -tumor necrosis factor α ; RANTES - regulated upon activation, novel T-cell expressed and presumably secreted (a molecule that is possibly secreted by activated T-lymphocytes); ICAM-1 - intercellular adhesion molecule - 1, LT-Leukotrienes.

- Thromboemboli of a. pulmonalis.
- Pneumothorax.
- Undetermined reason (approx. in 30% of all cases).

Respiratory infection is the reason for approximately 80% of COPD – exacerbations with a determined etiology. Often you can find *St. pneumoniae* in early and moderate stages of COPD (PEF1 > 50% from basic mean). In cases of severe and very severe course of the disease (PEF1 < 50% from basic mean) – gram-negative microflora (*H. influenzae*, *M. catharralis*, *P. aeruginosa* etc.) are common.

It is important to know that you can also find bacteria in expectorations of patients with a stable course. Investigations of protected bronchial biopsies of the lower respiratory tract show a colonization by microorganisms in approx. 30% of patients.

The mechanism through which microorganisms cause COPD exacerbations has not been well studied and remains unclear. It is well known that bacteria intensify the inflammation process in the respiratory tract in COPD exacerbations. This inflammation changes the local environment

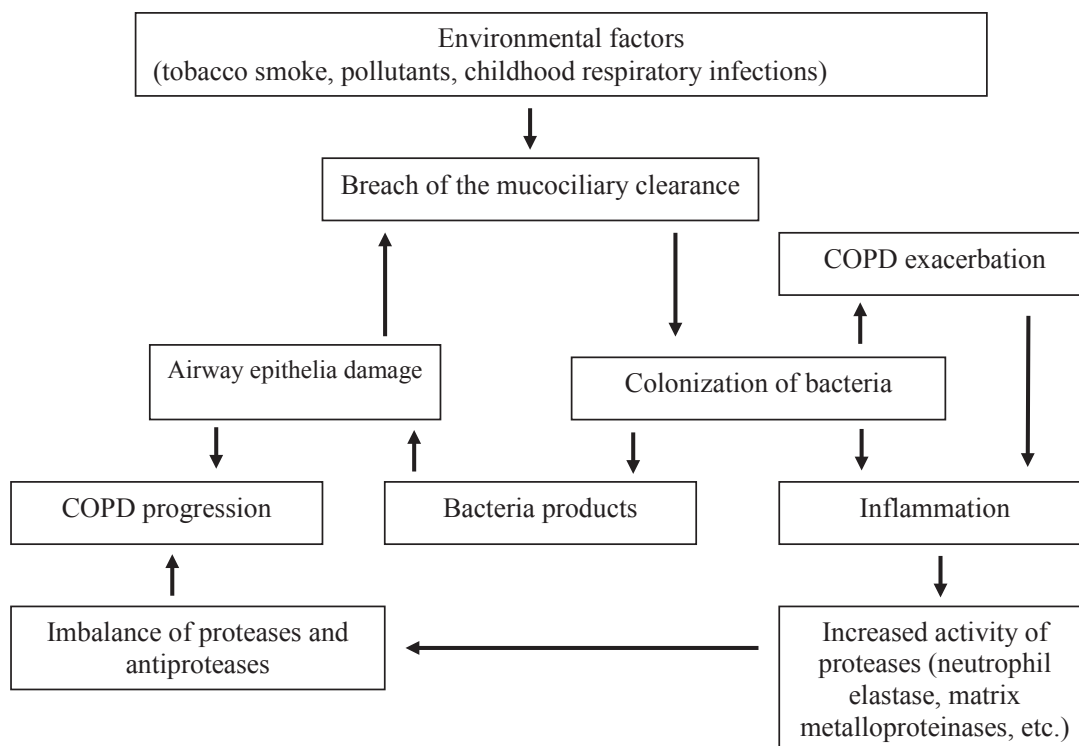


Fig. 1. The role of microorganisms in evolution of COPD (“vicious circle” conception).

Table 2

Characteristics of exacerbations of COPD

Indicators	The severity of exacerbation		
	Mild (Grade I)	Moderate (level II)	Severe (Grade III)
<i>History</i>			
Associated diseases	+	+++	+++
Frequent exacerbations	+	+++	+++
Severity of COPD	Easy / moderate	Moderately severe / severe	Severe / very severe
<i>Physical data</i>			
Hemodynamics	Stable	Stable	Stable / unstable
Involvement of respiratory muscles, tachypnea	No	++	+++
Persistence of symptoms after treatment	No	++	+++
<i>Diagnostic tests</i>			
Evaluation of blood oxygen saturation	Yes	Yes	Yes
The study of blood gases *	No	Yes	Yes
Chest X-ray	No	Yes	Yes
Clinical and biochemical blood tests **	No	Yes	Yes
Gram-stained smears and bacteriological analysis of sputum	No****	Yes	Yes
ECG	No	Yes	Yes
Measurement of drug concentration in blood serum	If possible	If possible	If possible
<p>Note: + is unlikely; ++probably, +++ highly likely; # diseases and syndromes associated with poor prognosis in exacerbations of COPD: Congestive heart failure, ischemic heart disease, diabetes, renal and hepatic failure, * including the values of PaO₂, pH and PaSO₂; **Biochemical analysis of blood include the determination of electrolytes and indicators of liver and kidney function; *** if the patient receives theophylline, warfarin, carbamezapine, digoxin; **** if the patient had recently received antibiotics.</p>			

in the airways and increases susceptibility to formation of new colonies of microorganisms that colonize the bronchial mucosa (*H. influenzae*) [6, 7, 8]. The role of microorganisms in the evolution of COPD is described by the hypothesis of “vicious circle”, which says that the damage of airways is the result of chronic infection. Meanwhile, chronic presence of pro-inflammatory mediators (interleukin 6, 8, TNF, leucotrien B4) decreases the efficiency of bronchial transit (fig.1).

Based on the recommendations of the experts of European and American Thorax Society, we distinguish mild, moderate and severe stages in the courses of COPD (tab. 2).

The treatment of exacerbations is as follows: broncholytics, systemic corticoids, antibiotics.

Antibacterial treatment is indicated in cases of clinical manifestations of exacerbation [5, 9]. Sputum analysis for the etiological factor isn't specific because the respiratory tract of such patients is often colonized by bacteria. Sputum analysis is recommended in cases of frequent exacerbations or in the presence of purulent expectoration when organisms resistant to traditional treatment are suspected.

The most common criteria for indication of antibacterial therapy were evaluated by Anthonisen et al. (1987) which describes three types of COPD exacerbations. The first type is characterized by intensification of dyspnea, increase in produced sputum volume and a change in the sputum characteristic, such as a purulent appearance. The second type includes two of these symptoms, the third – one. It is established that the antibacterial treatment is indicated in the first and the second types of COPD exacerbations.

The characteristics of COPD exacerbations

Scientifically proven advantages of antibacterial therapy have been described in the research literature:

- Decrease in the duration of an exacerbation episode
- Avoidance of hospitalization.

- Decrease in duration of temporary disability.
- Prophylaxis for pneumonia.
- Avoid progression of damage to the respiratory tract.
- Increase of remission duration.

The aim of antibacterial therapy is eradication of microorganisms, which provoke COPD exacerbations, thereby decreasing symptoms manifestation and increasing the stable course of the disease. The choice of drugs is made empirically, based on the particular course of a patient's disease as well as on the known resistance profiles of specific organisms. Different options of antibacterial therapy are showed in tab. 3.

In case of non-severe COPD exacerbations it is necessary to consider macrolides (Clarithromycin and Azythromycin) and beta-lactam antibiotics (Amoxycillin and Cephalosporines of the second and the third generation). Macrolides are very active towards *H. influenzae*, *Str. Pneumonia* and intracellular microorganisms (*C. pneumoniae*, *M. pneumoniae*). They have a high biological accessibility, deep penetration into lung tissue and into individual cells where they reach a high intracellular concentration. Clinical and bacterial efficacy of macrolides in COPD exacerbation is about 78-98% [9]. We previously obtained data which prove a high efficacy of azythromycin in treatment of COPD exacerbation. The results of our studies showed that therapy with azythromycin contributes to decrease in respiratory symptoms: cough decreased by 3 times (p < 0.001), quantity of expectoration – by 1.5 times (p < 0.001), and dyspnea – by 2 times (p < 0.001), while night-time symptoms disappeared almost completely. The regression of basic clinical manifestations is the common cumulative index which decreased by 3.2 times (p < 0.001). In patients who took standard therapy, the respiratory symptoms also decreased, but less significantly than in the experimental group. After a course of azythromycin therapy, cytosin indicators in induced expectoration decreased by 1.7 times, alveolar macrophages

Table 3

Variants of exacerbations of COPD and the choice of antibiotic therapy

Variants of exacerbations	Patient Characteristics	Current microorganism	A series Antibacterials	Alternative treatment
1. "Simple" exacerbations (without risk factors for microbial resistance to antibiotics)	Worsening of dyspnea and cough, increased sputum production with a purulent aspect. Any age, less than 4 exacerbations / year, the absence of concomitant diseases, FEV1 > 50% predicted	<i>Haemophilus influenzae</i> , <i>Haemophilus parainfluenzas</i> , <i>Moraxella catarrhalis</i> , <i>Streptococcus pneumoniae</i>	„New» macrolides (clarithromycin, azithromycin), 2nd and 3rd generations of cephalosporins, amoxicillin	Amoxicillin / clavulanic acid Respiratory fluoroquinolones
2.»Complicated» exacerbation (in the presence of risk factors for microbial resistance to antibiotics)	Symptoms of acute infection and one of the following criteria: age ≥ 65, more than 4 exacerbations / year, concomitant diseases of the cardiovascular system, FEV1 35-50% of predicted, the use of «home» oxygen therapy, antibiotics in the last 3 months.	<i>Haemophilus influenzae</i> , <i>Haemophilus parainfluenzas</i> , <i>Moraxella catarrhalis</i> , <i>Streptococcus pneumoniae</i> , <i>Klebsiella spp</i> , other bacteria gram-negative. High probability of microbial resistance to β-lactams	Respiratory fluoroquinolones (levofloxacin, moxifloxacin, and others), amoxicillin / clavulanic acid	Possible parenteral antibiotics and hospitalization of patients
3. Chronic purulent bronchitis (in the presence of risk factors for infection (<i>Ps. aeruginosae</i>))	More than 4 exacerbations / year, FEV1 < 35% predicted, possible bronchiectasis	Same microorganisms that are in group 2, <i>Pseudomonas aeruginosae</i> , multidrug resistant <i>Enterobacteriaceae</i>	Fluoroquinolones (ciprofloxacin), β-lactams (ceftazidime, and other means piperacillin/tazobactam with activity against <i>Ps. aeruginosae</i>)	-

decreased by 1.2 times. The level of IL-1α decreased on the 14-th day of treatment by 4.8 times, TNFα - by 4.5 times. IL-8 in blood decreased by 2.5 times.

Patients who received standard treatment without antibiotics also had a decrease in systemic inflammatory markers, however this was less significant as compared to the group that received antibiotics.

Probably the treatment effect with macrolides is determined by its non-antimicrobial activity. It is known these can modulate the activity of lymphocytes, modify the properties of trachea-bronchial secretions and decrease the intensity of systemic and local respiratory tract inflammation by changing the functional activity of neutrophils.

In recent years, fluoroquinolones with their antipneumococcus activity (levofloxacin, moxifloxacin etc.) have been found to be comparable with macrolides in the treatment of respiratory infections. As proof of the advantages of fluoroquinolones are used arguments such as: a) a high resistance level of *S. pneumoniae* and *H. influenzae* towards the macrolides which respectively corresponds to 30-50% and 35% improvement in different countries; b) a better response in clinical symptoms and bacteriological eradication, a lower relapse rate of COPD exacerbations and decreased long-term need for antibacterial treatment, although the letter has not been consistently supported in all studies.

Analyzing the mentioned results it is important to keep in mind that the local resistance of macrolides towards *S. pneumoniae* amounts to 2 - 6%. The resistance level of macrolides to *H. Influenza* is probably also low. This fact has been proven by a high clinical efficacy of clarithromycin observed in patients with COPD [1, 2, 4, 7]. Most of the research shows the efficacy of respiratory fluoroquinolones, regardless of the stage of COPD. It is also important to note that higher results in treating severe courses of the

disease were obtained when macrolides were not used as first line treatment (tab. 3).

Respiratory fluoroquinolones and protected penicillins are indicated in "complicated" exacerbations of COPD. These are indicated when there is presence of risk factors such as resistance of the microorganisms towards amoxicillin or macrolides. If there exists a high risk for *P. Aeruginosae* we recommend use of ciprofloxacin and beta-lactams given their activity against nosocomial pathogens (tab. 3). In most cases antibiotics are taken orally. Duration of antibacterial therapy in "non - complicated" exacerbations is 5 - 7 days, in "complicated" cases - 10 - 14 days until the complete disappearance of clinical symptoms of exacerbation [5, 9].

The dosage regimen of broncholytics is given in tables 3 and 4. In case of mild and severe exacerbations of COPD, especially in older patients, it is necessary to administer nebulizer therapy.

Because of the difficulties in dosage and the many side effects of theophylline, we suggest using these drugs as secondary treatment when the inhaled broncholytics aren't effective enough. However, no everyone agrees with this point of view. Probably the use of these drugs is possible only by respecting the indication rules and monitoring the concentration of theophylline in the blood. The best known of this class is Euphyllin which contains theophylline (80%) dissolved in ethylenediamine (20%). The schedule of its dosage is shown in tab. 4. It is important to mention that theophyllin has to be introduced only intravenously. Theophylline administration over a long period of time is contraindicated because there is a danger of overdose.

Systemic glucocorticoids are effective in treatment of complications of COPD. These drugs decrease the convalescence time and contribute to a more rapid regeneration of lung functions. They are indicated together with broncho-

lytics when FEV1 is < 50% from normal values. Normally it is recommended 30 – 40 mg prednisone by mouth or the equivalent intravenous methylprednisolone dose for 10 – 14 days. Treatment for a longer period of time doesn't lead to a higher effectiveness but increases the risk of development of side effects. In the last few years' data appeared about the possibility of using inhalational glucocorticoids (Budesonide, introduced with nebulizers, as an alternative to systemic glucocorticoids in the treatment of COPD exacerbations.

Table 4

Dosage of Euphyllin by intravenous introduction

Particularities of introduction	Doses
Loading dose (<i>intravenously</i> infused over 20 min): For patients who didn't get theophylline For patients who got theophylline	240-250 mg Introduction is contraindicated
Maintenance dose (<i>intravenously</i> infused over 3 – 5 h)	
Smokers	0.9 mg/kg/h
Nonsmokers	0.6 mg/kg/h
Patients with a low theophylline clearance	0.25 mg/kg/h
Daily doses of theophylline	0.75-1.5 g

Patients with light exacerbations can be treated in an ambulatory setting. Patients with moderate or severe levels of COPD have to be hospitalized. Indications for directing the patients to specialized departments are as follows:

1. Significant increase in symptom intensity (e.g. appearance of dyspnea in rest).
2. Conventional treatment is not effective.
3. Appearance of new symptoms (eg. cyanosis, peripheral edema).
4. Severe concomitant diseases (pneumonia, cardiac arrhythmia, congestive heart failure, diabetes, renal and kidney insufficiency).
5. New onset of abnormal heart rhythm.

6. Older age.
7. Inability to provide adequate medical care in an outpatient setting.
8. Difficulty of diagnosis.

Algorithms for treatment of exacerbations of COPD are shown in figures 2-4.

In severe exacerbations of COPD patients have to be hospitalized in an intensive care unit, the indication for which are:

1. Severe shortness of breath, not relieved by bronchodilators.
2. Impaired consciousness, coma.
3. Progressive hypoxemia (PaO2 < 50 mm Hg), hypercapnia (PaCO2 > 60 mm Hg) and/or respiratory acidosis (pH < 7.25), despite the use of oxygen-therapy and noninvasive ventilation.

Criteria for patient discharge from hospital after a COPD exacerbation:

- a) requirement for inhaled short-acting adreno-agonists does not exceed more than every 4 hours.
- b) the patient can ambulate on their own, eat and sleep without frequent nighttime awakenings from shortness of breath;
- c) stable state for 12-24 hours;
- d) stable blood gas analysis for 12-24 hours;
- e) patient and responsible family members have a complete understanding of proper medication use;
- f) there are arrangements for further observation and treatment at home.

In the next 4-6 weeks the patient should be re-examined by a doctor to evaluate adaptation to life and correct inhalation technique, as well as analysis of pulmonary function tests (PFT), blood gas or oxygen saturation (to decide if a long-term oxygen therapy is necessary). Further treatment may be indicated at this time.

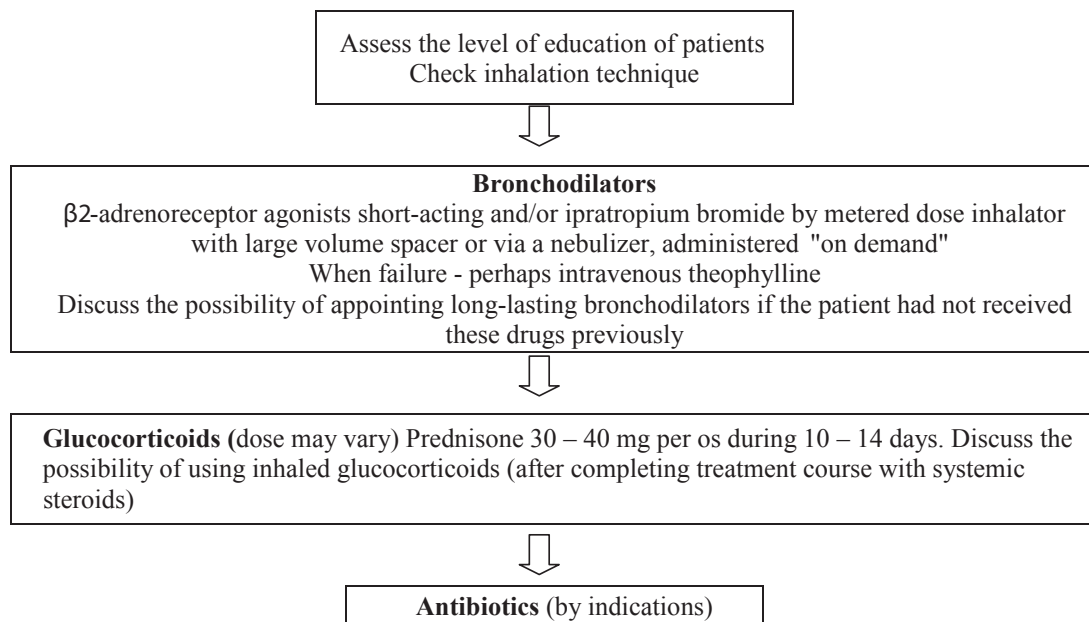


Fig. 2. Ambulatory treatment of patients with mild exacerbations.

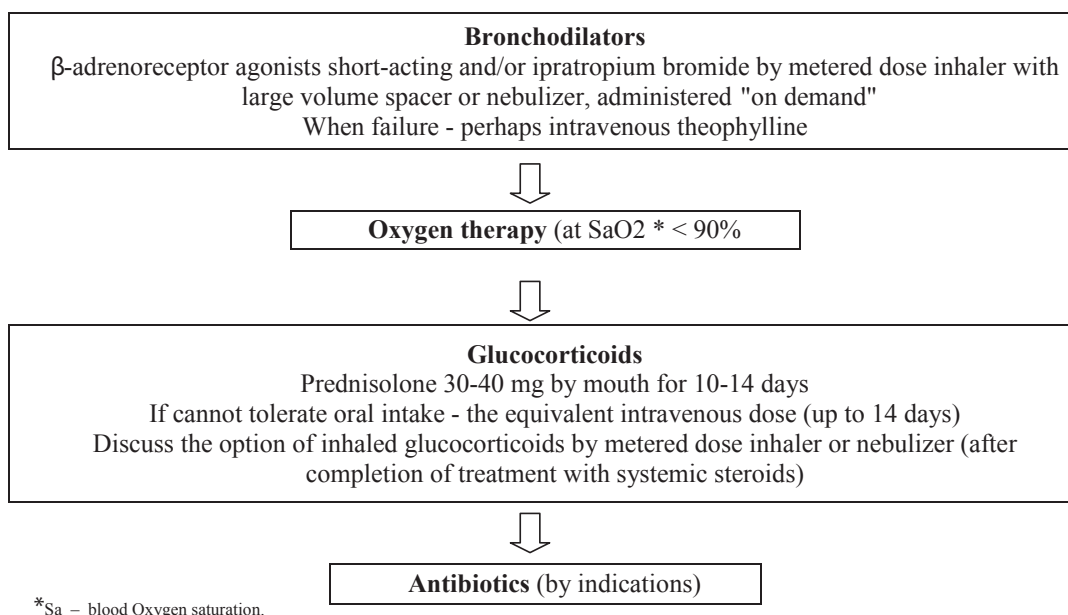


Fig. 3. Treatment of moderate exacerbations of COPD in hospitalized patients.

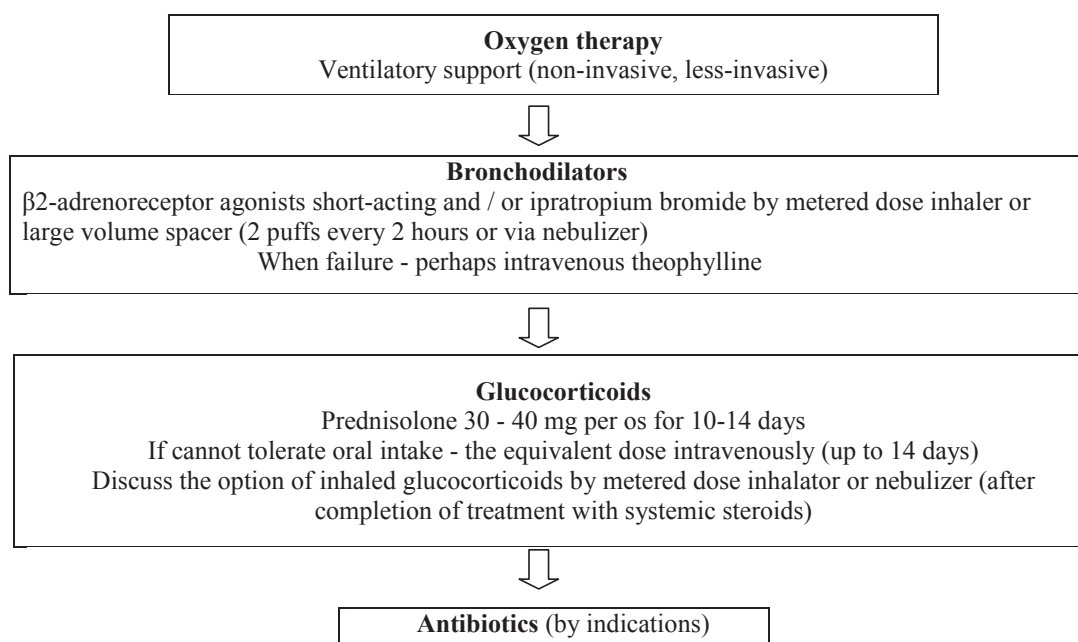


Fig. 4. Treatment of severe exacerbations of COPD in the emergency department.

Table 5

Inhalative broncholytics used for COPD exacerbation treatment

Drug	Release form	Doses
Salbutamol (Ventholyn nebullets, Salgym, Steri- neb-Salamolol etc.)	Solution for nebulizers 2.5 and 5 mg/ml Dosed aerosol with spacer (100 mcg/doses)	2.5-5 mg every 4-6 h in regime «on demand» 2-4 inhalations every 4-6 h in regime «on demand»
Fenoterol (Berotec and Berotec H)	Solution for nebulizers 1 mg/ml Dosed inhaler with spacer (100 mcg/doses)	0.5-1.0 mg every 4-6 h in regime «on demand» 2-4 inhalations every 4-6 h in regime «on demand»
Ipratropium bromide (Atrovent, Atrovent H)	Solution for nebulizers 0.25 mg/ml Dosed inhaler with spacer (40 mcg/doses)	0.25-0.5 mg every 6-8 h in regime «on demand» 2-4 inhalations every 6-8h in regime «on demand»
Ipratropium bromide and Fenoterol (Berodual and Berodual H)	Solution for nebulizers (in 1ml 0.25 mg ipratropium bromide and 0.5 mg fenoterol) Dosed inhaler (in 1 inhaler. 20 mcg ipratropium bromide and 50mcg fenoterol) with spacer	2-4 mg every 6-8 h in regime «on demand» 2-4 inhalations every 6-8 h in regime «on demand»

For the prevention of exacerbations bronchodilators and inhaled glucocorticoids are used in combination with long-acting β_2 -adrenomimetics (severe and very severe COPD). Yearly influenza vaccination is highly recommended.

In conclusion, it should be noted that if the antibiotic therapy is chosen correctly for the individual, it reduces the duration of hospital stay and the costs associated with medical care.

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The Modification of the Serum Ascites Lymphatic Albumin Gradient in Liver Cirrhotic Decompensated Patients with Ascitic Syndrome

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Abstract

The study involved 23 patients with decompensated liver cirrhosis and ascitic syndrome. This trial was designed to determine the value of serum-ascites and lymphatic albumin gradients. We established diminution of the albumin ascites-lymphatic gradient in relationship with the evolution of the ascitic syndrome. We introduce the notion of serum/ascites/lymphatic albumin gradient and its significance on parameters of the evolution of the ascitic syndrome. It is required to validate the clinical application of the gradient in following studies.

Key words: ascitic syndrome, serum ascitic lymphatic albumin gradient.

Изменения альбуминового градиента (асцит, плазма, лимфа) у декомпенсированных больных циррозом печени и асцитическим синдромом

В настоящую работу включены 23 больных с декомпенсированным циррозом печени и асцитическим синдромом. Исследование было посвящено изучению и оценке альбуминового градиента (асцит, плазма, лимфа). Установлено уменьшение альбуминового градиента асцит-лимфа в соотношении с развитием асцитического синдрома. Впервые предложена терминология альбуминового градиента (асцит, плазма, лимфа), однако его значение, как критерия развития асцитического синдрома, требует уточнения в дальнейших исследованиях.

Ключевые слова: асцитический синдром, градиент концентрации альбумина сыворотка-асцит.

Introduction

According to literature data, 4-5% of the global population shows disturbances of liver functions, of which about 10-20% are caused by viral hepatitis, toxic hepatitis or ethanol alcohol, that within 10-20 years lead to the

evolution of cirrhosis liver [1], which inevitably leads to a high rate of complications such as variceal hemorrhage either cirrhotic hypersplenism with coagulopathy in progress or ascitic syndrome. Thus, N. Fisher et al. notes that in Great Britain alone, during the years 1993-2000,